

Capillary Fragility and Doxium A Controlled Clinical Trial

R. Rasch

Second University Clinic of Internal Medicine, University of Aarhus, Denmark.

Received: February 9, 1973, and in revised form: July 13, 1973

Summary. The effect of Doxium on capillary resistance has been investigated in a 7 month double-blind clinical trial on 16 long-term diabetics with retinopathy. Quantitative measurements were performed every 5–6 weeks. The drug showed no effect on capillary resistance.

Key words: Capillary fragility, Doxium, calcium-Dobesilate, diabetes mellitus, diabetic retinopathy.

In 1968 Sévin and Cuendet [1] reported on the use of Ethamsylate or Dicyclic® (diethylammoniumparadihydroxybenzensulfonate) in diabetic patients with retinopathy and reduced capillary resistance. They found that Ethamsylate caused a significant rise in capillary resistance as measured on the skin as well as on the conjunctiva of the eye in all of 19 patients treated for 3 months.

A similar synthetic drug, Calcium-Dobesilate or Doxium® (calciumdihydroxybenzensulfonate) has now been brought on the market. It is said to act identically, but to be much more effective on diminished capillary resistance, capillary hyperpermeability and diabetic retinopathy, resulting in a decrease in the incidence of haemorrhagic episodes and causing improvement in visual acuity.

Sévin and Cuendet [2, 3] have reported that Doxium 500 mg daily over a period of 3–6 months improves the capillary resistance in diabetics as measured once a month on the conjunctiva of the eye. The rise in capillary resistance is stated to be constant and significant from any measurement to the next one and in all subjects. All patients reached normal values after 4 months of treatment.

The authors also examined the patients ophthalmoscopically at regular intervals during treatment. There were no haemorrhagic episodes after 3–4 months of treatment, and the authors conclude that the drug has “preventive and curative effects”. There was no control-group.

Favre [4] has shown the same effect on the capillary resistance in diabetics by measurements on the skin. Ophthalmoscopically 8 were estimated to have improved, 5 to have been unchanged and 2 to have worsened.

The present report concerns the result of a controlled clinical trial on the effect of Doxium on the

skin capillary resistance, carried out in a series of long-term diabetic patients with mild (simple) retinopathy.

Method

Measurements

Skin capillary resistance was measured with the negative suction cup technique, described by Christensen and Terkildsen [5]. A plastic suction cup with an inner diameter of 7 mm and an outer of 13 mm was used.

A negative pressure of 50 mm Hg was applied instantaneously, and continued for one minute, the pressure being read on a mercury column. If, after removal of the cup, no petechiae have appeared a negative pressure of 75 mm Hg was applied to the same spot for one minute. The test continues in this way, increasing the negative pressure by 25 mm Hg until one or more petechiae appear. The pressure at which this occurs was noted as the capillary resistance of that particular spot. The whole procedure was repeated 10 times in 2 longitudinal rows on the anteromedial side of the upper part of the left arm. The capillary resistance is defined as the mean of the 10 single measurements.

All measurements were performed in the same room with the patients and the investigator in the same position every time. The artificial light was the same every time coming from the same direction. The investigations were performed at the same hour of the day for each patient.

The major part of the investigations was performed at a room temperature of approximately 24°C, but on a few cases, however, there was a variation within 23–26°C. Before capillary resistance measurements were performed skin temperature was measured on the anteromedial side of the left upper part of the arm.

As was to be expected there was a positive correlation between room temperature and the temperature of the skin. However, inside this narrow range of temperature there was no relationship with capillary resistance.

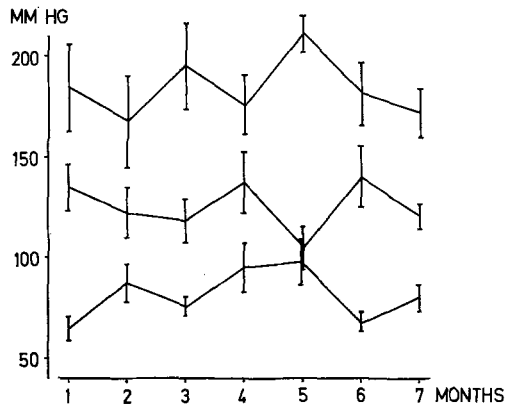


Fig. 1. Capillary resistance in 3 patients; average values and SEM

Fig. 1 indicates the variability of the individual measurements and the relative stability of the average value in the course of time in 3 patients from the placebo group.

Selection of Patients

Separation into Groups

Sixteen patients with diabetic retinopathy were selected. They all had retinal haemorrhages, but none had bleeding into the vitreous body, and none had vascular proliferation. The patients were less than 65 years old and had suffered from diabetes for more than 10 years (10 to 32 years, mean 21). All were on insulin treatment except one, who was treated with tolbutamide and glibenclamide. Serum creatinine levels were normal. All had normal blood pressure. None of the patients were on steroid treatment and none of them had skin diseases. In fertile women the investigations were not performed during menstruation or for 3 days before.

The allocation of the patients to Doxium or Placebo was done only with regard to capillary resistance.

Mean capillary resistance in the Doxium group was $91 \text{ mm Hg} \pm 17 \text{ (SD)}$ and in the Placebo group $101 \pm 40 \text{ (SD)}$. With a difference of 10 mm Hg this is not statistically significant ($2 p > 0.2$).

Mean age was 48 years in both groups.

Mean duration of diabetes was 25 years in the Doxium-treated group and 17 years in the Placebo group, the difference not being statistically significant ($2 p > 0.2$).

Mean blood pressure was 144/86 in the Doxium group and 148/93 in the Placebo group.

Two patients had proteinuria, one in each group.

Doxium tablets, 250 mg twice a day, and Placebo tablets of practically the same colour were given to the patients in closed envelopes. The investigator did not know if a patient was on Doxium or on Placebo or which patients formed a group. Each capillary resistance measurement was done independently, results from earlier measurements in the same patient not being available at the time when the test was performed. No results were calculated till at the end of the experiment in all patients. An extra pre-trial value was taken in each patient, and after the trial had started measurements were performed with intervals of 5–6 weeks (mean 5.5). Haemoglobin, sedimentation rate, leucocyte count, transaminases, serum creatinine and blood pressure were measured in each patient before and after the trial. They showed no changes, except in one patient, in the control group, whose serum creatinine rose from 1.3 to 2.5 mg%.

Every time measurements were performed investigations were made to find out if the patients remaining tablets corresponded to the calculated number. It did so within very narrow limits.

Results

It appears from Fig. 2 that the average capillary resistance remained unchanged in the control group. Capillary resistance did not improve in the Doxium-treated group; on the contrary, the average curve shows a slight fall. However, this fall is not statistically significant. Paired comparison between the mean of the 2 initial values and the mean of the two last values gives a $2 P$ value > 0.05 ($= 0.0521$).

The present study was planned as an investigation of the effect of Doxium on skin capillary resistance. However, simple ophthalmoscopic observations were included before and after the trial and if the patients reported that acute change of vision had occurred. Before and at the conclusion of the experiment a map was carefully drawn of the retina after instillation of a mydriatic. In 14 patients no major changes could be ascertained. In three eyes of two patients large vitreous hemorrhages occurred, seriously affecting the vision. The first bleeding occurred after four months of treatment and the others after more than four months of treatment. There was very little improvement in vision within the next three months.

All bleeding occurred in patients who turned out to have been treated with Doxium.

Discussion

Capillary resistance is reduced in long-term diabetic patients with retinopathy, glomerulosclerosis and other evidence of diabetic angiopathy [6, 7]. Profuse bleeding from retinal vessels is often the

immediate cause of blindness in diabetic retinopathy. Reduced capillary resistance is presumably an important causal factor in the development of retinal haemorrhage.

There are only few therapeutic measures available in serious diabetic retinopathy with threatening blindness. Pituitary ablation has been shown to inhibit the development of the retinopathy [8, 9], and it

tions, e.g. Rutin and other flavonoids, have not been confirmed or have seemed very doubtful.

Astonishing effects on capillary resistance and retinal abnormalities have been reported recently with the use of Doxium. Unfortunately, the present controlled clinical trial has shown that Doxium has no effect on capillary resistance. The fact that in our series retinal haemorrhages occurred in a few patients of the Doxium group, and not in the Placebo group, does not prove, of course, that this drug is dangerous. On the other hand there is no reason to believe that it has any beneficial effect on diabetic retinopathy.

Acknowledgement. Doxium tablets and Placebo was provided by the producers the OM Lab., Geneva.

References

1. Sévin, R., Cuendet, J.F.: Résistance capillaire et rétinopathie diabétique. *Ophthalmologia* **155**, 186–193 (1968)
2. Sévin, R., Cuendet, J.F.: Calcium Dobesilate in diabetic retinopathy. *Ophthalmologia* **159**, 126–135 (1969)
3. Sévin, R., Cuendet, J.F.: The action of Calcium Dobesilate on capillary permeability in diabetes. *Ophthalmologia* **162**, 33–40 (1971)
4. Favre, M.: Le traitement de la rétinopathie diabétique et de l'hémorragie récidivante du vitre par le Dobesilate de Calcium. *Ophthalmologia* **161**, 389–393 (1970)
5. Christensen, N.J., Terkildsen, A.B.: Quantitative measurements of skin capillary resistance in hypophysectomized long term diabetics. *Diabetes* **20**, 297–301 (1971)
6. Hanum, S.: Diabetic Retinitis. *Acta ophthalmologica supplement* **16**, (1939)
7. Hunter, P.R., Bloom, A., Kelsey, J.H., Porter, R.: Cutaneous capillary resistance and retinal haemorrhage in diabetes. *Diabetologia* **7**, 20–24 (1971)
8. Lundbaek, K., Malmros, R., Andersen, H.C., Rasmussen, J.H.: In: Symposium on the Treatment of Diabetic Retinopathy. M.F. Goldberg and S.L. Fine (Eds.). Public Health Publication number 1890, Washington, D.C. pp. 291–311 (1969)
9. Oakley, N.W., Joplin, G.F., Kohner, E.M., Fraser, T.R.: In: Symposium on the Treatment of Diabetic Retinopathy. Public Health Publication number 1890. M.F. Goldberg and S.L. Fine (Eds.). Washington, D.C. pp. 317–329 (1969)

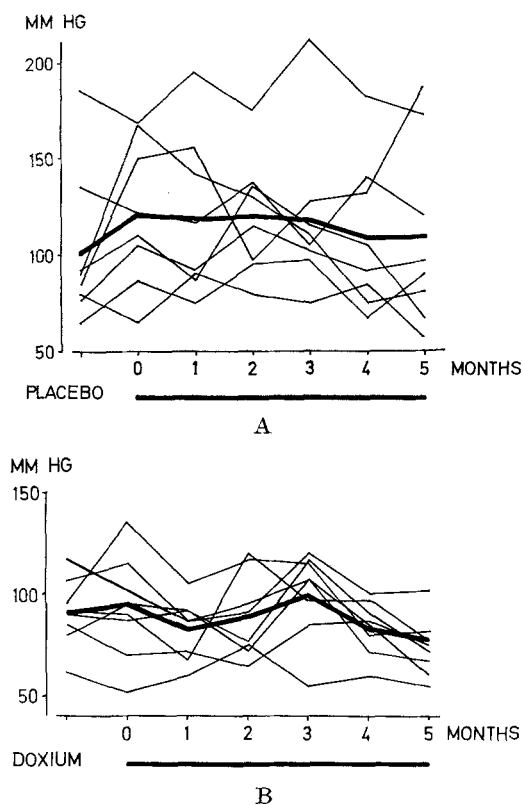


Fig. 2. A., B. Mean capillary resistance during the 7 months period. The 2 first measurements are pre-trial values. Upper part control group, lower part Doxium group. Mean normal value 200 mm Hg

normalizes the capillary resistance [5]. With photo- or laser coagulation abnormal areas of the retina can undoubtedly be erased, but there is still no convincing proof that this type of treatment adds to the years of useful vision.

A drug claimed to normalize capillary resistance and to ameliorate diabetic retinopathy is therefore of great interest. Such claims about earlier prepara-

Dr. R. Rasch
Second Clinic of Internal Medicine
Aarhus University School of Medicine
Nørrebrogade
DK-8000 Aarhus
Denmark